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OWD Docket No. 14598-41 (Was: BEH-7443)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	**K. Kasper et al.**	**Examiner:**	**M.E. Ceperley**
Serial No.:	**09/368,010**	**Group Art Unit:**	**1641**
Filed:	**August 3, 1999**	**Docket:**	**14598-41**
Due Date:	**May 25, 2002**	**Date Mailed:**	**April 24, 2002**

Title: **MONOCLONAL ANTIBODIES TO TACROLIMUS AND IMMUNOASSAY METHODS FOR TACROLIMUS**

I hereby certify that this correspondence and identified enclosures are being deposited with the United States Postal Service, first class mail, postage prepaid, under 37 C.F.R. 1.8 on the date indicated, and is addressed to: Box AF, Commissioner for Patents, Washington, D.C. 20231 on **April 24, 2002.**

Joy Johnson

Joy Johnson

BRIEF FOR APPELLANT UNDER 37 C.F.R. § 1.192

Box AF
Honorable Commissioner for Patents
Washington, D.C. 20231

Gentlemen:

In furtherance of the appeal filed March 25, 2002, Appellant hereby submits his appeal brief in triplicate as follows:

I. REAL PARTY IN INTEREST

The real party in interest is Dade Behring Marburg GmbH, a German corporation, whose primary place of business in the United States is Deerfield, Illinois.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

III. STATUS OF CLAIMS

Claims 11-12, 31-33, 50-51, and 61 are pending and are appealed. Claims 1-10, 13-30, 34-49, 52-60, and 62-82 had been previously cancelled.

IV. STATUS OF ANY AMENDMENTS FILED SUBSEQUENT TO FINAL REJECTION

The amendment filed on January 16, 2002, cancelling claims 1-10, 13-30, 34-49, 52-60, and 62-82, has been entered. The Advisory Action, mailed March 6, 2002, indicates that claims 11-12, 31-33, 50-51, and 61 were pending. There were no other amendments filed subsequent to final rejection.

V. SUMMARY OF THE INVENTION

The present invention is directed to monoclonal antibodies that specifically bind the immunosuppressive agent tacrolimus, also known as FK-506 or FR-900506. Tacrolimus is a macrolide isolated from *Streptomyces tsubakiensis* that has antimicrobial activity and immunosuppressive activity.

The immunosuppressive activity of tacrolimus is particularly important and has led to the increasingly wide use of this drug. Immunosuppression is used clinically in a number of contexts, most importantly in preventing rejection in organ transplantation.

Immunosuppressive drugs are also administered in prevention of Rh hemolytic disease of the newborn and in the treatment of autoimmune disorders. Tacrolimus can be administered intravenously in a short or continuous infusion or orally.

Tacrolimus, like other immunosuppressive agents, has a spectrum of toxicity. The major toxicity associated with clinical use of the drug is nephrotoxicity. In addition, neurotoxicity can develop, associated with headache, tremor, insomnia, pain, or other symptoms. Additionally, gastrointestinal toxicity manifested by diarrhea or nausea can develop, as can cardiovascular toxicity manifested by hypertension. Additionally, metabolic toxicity can develop as manifested by the development of such symptoms as hyperkalemia, hypomagnesemia, or hyperglycemia. In addition, long-term immunosuppression with tacrolimus can produce increased risk of all types of infections, not only infections caused by the usual bacterial, viral, and fungal pathogens, but also various opportunistic infections. Additionally, there is an increased risk of lymphomas and related malignancies associated with the administration of tacrolimus.

The potency and the spectrum of toxicities of tacrolimus requires sensitive, reproducible, and reliable methods for monitoring the blood concentration of tacrolimus after administration to a patient. Excessively high levels of tacrolimus can lead to the side effects and toxicities recited above, while excessively low levels of tacrolimus can result in rejection of the transplanted organ or failure to treat the disease process characterized by an immune response. It is therefore exceedingly important that methods used for monitoring the blood concentration of tacrolimus be sensitive enough to detect low concentrations of tacrolimus. It is also important that such methods be reliable and reproducible, and avoid interference from compounds such as metabolites of tacrolimus.

The development of a reliable immunoassay for tacrolimus is complicated by the fact that tacrolimus has a number of metabolites that are found in the blood of an individual being treated with tacrolimus. The conversion of tacrolimus to these metabolites involves

demethylation, hydroxylation, and ring formation. It is therefore important that antibodies to tacrolimus have as little cross-reactivity with these derivatives as possible.

The inventors have found that tacrolimus, when derivatized in the non-binding domain, can be coupled to a high molecular weight carrier such as a protein for immunization to produce antibodies. The resulting antibody-producing cells can be used to generate monoclonal antibodies by cell fusion, such as by use of the standard Kohler-Milstein process. The resulting monoclonal antibodies have desirable properties, including high affinity and reduced cross-reactivity with metabolites of tacrolimus.

Specifically, tacrolimus is derivatized at position 22 by reaction with carboxymethoxylamine to produce a carboxymethyl oxime derivative. The carboxymethyl oxime derivative is then activated to produce a reactive N-hydroxysuccinimide ester. The reactive N-hydroxysuccinimide ester is then reacted with a carrier protein for immunization.

The monoclonal antibodies produced by this process have a binding affinity for tacrolimus of about 3.7×10^9 liters/mole. The antibodies cross-react with 13-demethyl tacrolimus. The antibodies have less than about 8% cross-reactivity to all of the following tacrolimus metabolites: 15-demethyl tacrolimus; 31-demethyl tacrolimus; 13,31-didemethyl tacrolimus; 15,31-didemethyl tacrolimus; and 12-hydroxy tacrolimus.

VI. ISSUES PRESENTED FOR REVIEW

The following issue is presented for review: whether claims 11-12, 31-33, 50-51, and 61 were properly rejected under the first paragraph of 35 U.S.C. § 112 for lack of enablement. Appellants maintain that the rejection was improper and was contrary to established legal standards governing enablement.

VII. GROUPING OF CLAIMS

In consideration of this appeal, claims 11-12, 31-33, 50-51, and 61 are to be considered together. The antibody conjugates of claims 31-33, the immunoassay methods of claims 50-51, and the test kit of claim 61 are all enabled if the antibody of claim 11 is enabled. Standard methods are used to produce the antibody conjugates of claims 31-33 from the antibody of claim 11 by coupling the antibody to one of a number of detectable labels that are commonly used in immunochemistry. The immunoassay methods of claims 50-51 are standard methods in the art, using the antibody of claim 11. The test kit of claim 61 is assembled by standard methods and includes the antibody of claim 11; the other components are standard in the art.

VIII. ARGUMENT

All claims are enabled and can be practiced by one of ordinary skill in the art without undue experimentation. Accordingly, there is no basis for a rejection under the first paragraph of 35 U.S.C. § 112 and the Board of Patent Appeals and Interferences is respectfully requested to reverse this rejection.

It was stated in the rejection made by the Examiner that the specification was inadequate to enable one of ordinary skill in the art to produce a monoclonal antibody having the specific characteristics recited in claim 11, namely, specific affinity and cross-reactivity limitations. The Board of Patent Appeals and Interferences is respectfully requested to reverse this rejection, because sufficient enablement exists to meet the legal standard required by the first paragraph of 35 U.S.C. § 112 and the governing case law.

To summarize briefly, Example 1 describes the preparation of carbon-22 substituted derivatives of tacrolimus. These derivatives include a monooxime of tacrolimus

(page 25, line 18 to page 26, line 13). The monooxime of tacrolimus was prepared by reacting tacrolimus with carboxymethoxylamine hydrochloride.

Example 2 describes the preparation of a tacrolimus-keyhole limpet hemocyanin conjugate. The tacrolimus monooxime is reacted with a coupling agent, the carbodiimide 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDAC). The tacrolimus monooxime that has been activated by reaction with the EDAC is then added to keyhole limpet hemocyanin to produce the tacrolimus-keyhole limpet hemocyanin conjugate (page 26, line 20, to page 27, line 9).

The preparation of monoclonal antibodies to tacrolimus using the tacrolimus conjugate with keyhole limpet hemocyanin is described in Example 5. The immunization schedule and immunogens used, including the adjuvants, are described. The adjuvant used was monophosphoryl lipid A and synthetic trehalose dicorynomicolate adjuvant for the first immunization and for the first booster immunization (page 29, lines 16-25).

The fusion was performed by standard methods using a non-secreting murine myeloma (page 29, lines 27-28). Cloning was performed by standard methods (page 29, line 30).

The screening was performed by a standard reverse ELISA immunoassay procedure in which the antibodies are bound to the plates by being captured by polyclonal goat anti-mouse IgG, and then the antibodies are reacted with an enzyme conjugate of tacrolimus covalently coupled to the enzyme glucose-6-phosphate dehydrogenase, which produces color when it reacts with a chromogenic substrate. These procedures are standard in the art and are described in detail in the specification at page 30, lines 1-25.

A monoclonal antibody having these characteristics was isolated and described. The properties of this monoclonal antibody are described at page 30, line 27, to page 31, line 3 of the specification.

Reversal of the rejection is sought on the following grounds:

Firstly, the burden of the Patent and Trademark Office to show nonenablement has not been met for the rejection made in this application. As a matter of Patent Office practice, the specification must be taken as in compliance with the first paragraph of 35 U.S.C. § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support. In re Marzocchi, 439 F.2d 220, 169 U.S.P.Q. 367 (C.C.P.A. 1971). Moreover, properly reasoned and supported statements explaining any failure to comply with the enablement requirement of § 112 are a requirement to support such a rejection. In re Wright, 999 F.2d 1557, 27 U.S.P.Q. 2d 1510 (Fed. Cir. 1993).

The Office Actions made in this application have provided no evidence or reasoning whatsoever that would support a conclusion of lack of enablement or undue experimentation of the subject matter of these claims. This applies to the first, non-final Office Action, the second, final Office Action, and the Advisory Action. There was absolutely no suggestion, for example, that the derivatization and coupling process with tacrolimus would not work as described, that polyclonal antibodies could not be produced by immunization using adjuvants as described, that the fusion process using a standard non-secreting fusion partner would not work, that the cloning process would not work, or that the screening process would not work. In fact, there is no objective or empirical basis whatsoever for a conclusion of nonenablement in view of the working example provided in the specification. This working example resulted in a monoclonal antibody having the properties of claim 11.

Even should considerable experimentation be required, this does not constitute "undue experimentation" if it is routine and the worker is given sufficient guidance. "[A]n

extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." In re Colianni, 561 F.2d 220, 224, 195 U.S.P.Q. 150, 153 (C.C.P.A. 1977).

Enablement can be present if one of ordinary skill in the art can modify the teachings of the specification to practice the claimed invention by following well-established guidelines. See In re Bundy, 642 F.2d 430, 434, 209 U.S.P.Q. 48, 51-52 (C.C.P.A. 1981) (disclosure sufficient to enable one skilled in the art to use claimed analogues of naturally occurring prostaglandins even though specification lacked any examples of specific dosages, because specification taught that novel prostaglandins had certain pharmacological properties and possessed activity similar to known E-type prostaglandins).

The Office Action had previously laid great stress on the fact that only one monoclonal antibody having the required characteristics was recited in the specification. Applicants would like to respectfully remind the Patent and Trademark Office that there is no requirement for even a single working example even in allegedly unpredictable technologies, such as immunochemistry. In re Strahilevitz, 668 F.2d 1229, 212 U.S.P.Q. 561 (C.C.P.A. 1982). The fact that only a single monoclonal antibody that met the requirements of the claims was recited in the specification cannot be used to support a conclusion of undue experimentation or lack of enablement.

A certain amount of routine experimentation associated with the optimization of the Kohler-Milstein monoclonal antibody production process does not constitute undue experimentation. It is well recognized that a certain amount of routine repetition is required for monoclonal antibody production by cell fusion according to this process and that all attempts to produce monoclonal antibodies do not necessarily succeed. Such a degree of repetition and routine experimentation does not constitute undue experimentation in this technology. Johns Hopkins University v. CellPro, Inc., 152 F.3d 1342, 47 U.S.P.Q. 2d 1705 (Fed. Cir. 1998). In Johns Hopkins University, defendant CellPro claimed that the patent belonging to Johns

Hopkins, claiming a monoclonal antibody that bound a specific lymphoid system antigen identified as CD34, was invalid for lack of enablement. CellPro argued that the specification did not teach one skilled in the art to make antibodies that bound to the CD34 antigen other than one antibody, specifically disclosed in the specification, that was referred to as the anti-My-10 antibody. CellPro further asserted that the specification was insufficient to enable one of ordinary skill in the art to make and use the broader genus of claimed antibodies without undue experimentation.

The court rejected this argument, despite several failures at reproducing the claimed invention alluded to by CellPro. These failures were disregarded because many of them were by inexperienced workers, such as undergraduate students, who had little or no experience in producing monoclonal antibodies and who, in many cases, had not successfully made any monoclonal antibody. The court emphasized that the test for lack of enablement was whether "one of ordinary skill in the art would be unable to make the claimed invention without undue experimentation." Id. at 1360, 47 U.S.P.Q. 2d at 1718 (emphasis in the original). These inexperienced students were considered to lack ordinary skill in the art, and their failures were disregarded.

Secondly, the court disregarded an expert declaration that stated that the expert was unable to make an anti-CD34 monoclonal antibody. This evidence, too, was disregarded, as the screening technique described in the specification was not used.

Finally, the court stated that evidence from a second expert that anti-CD34 monoclonal antibodies were more difficult to make than certain other monoclonal antibodies was not sufficient to lead to a conclusion of undue experimentation. The court stated that any difficulty in producing such monoclonal antibodies was due to the fact that the Kohler-Milstein technique "was not foolproof" and that "success with this technique commonly required repetition." Id. at 1360, 47 U.S.P.Q. 2d at 1718. The lack of certainty was not attributable to a failure of disclosure in the patent in suit. The resulting experimentation was not "undue

experimentation" in the context of the invention. There was some information that the relative difficulties seen in producing monoclonal antibodies to the CD34 antigen was due to the relatively weak immunogenicity of the particular cell line used as an immunogen. These monoclonal antibodies were produced by first immunizing an antibody-producing mammal with an intact cell line. Id. Thus, the court granted summary judgment against defendant CellPro on the issue of enablement, holding, as a matter of law, that the enablement requirements of the first paragraph of § 112 were satisfied.

The degree of unpredictability must be considered in the context of the invention and the knowledge of those skilled in the art. Even broad claims can be enabled if the subject matter of the claims is such that the unpredictability of the subject matter of the claims is minimized. See In re Vaeck, 20 U.S.P.Q. 2d 1438, 1444-45 (Fed. Cir. 1991) (claims directed to expression of chimeric genes in specific genera of cyanobacteria allowable even though claims not limited to expression of genes encoding particular *Bacillus* proteins in view of extensive understanding in the prior art of toxicity of *Bacillus* proteins).

The monoclonal antibodies that are the subject of the present application are produced by initially immunizing an animal with an isolated immunogen, tacrolimus, coupled to a carrier. By contrast, the monoclonal antibodies that were at issue in CellPro were produced by initially immunizing an animal with an intact cell line. The use of an intact cell line as an immunogen introduces additional variables because of the large number of proteins and glycoproteins, as well as other surface antigens, that can produce an immune response. Yet, despite these variables, one working example was deemed sufficient in Johns Hopkins University. If one working example is sufficient under the fact pattern of Johns Hopkins University, it certainly should be sufficient where, as here, a purified immunogen is used instead of an intact cell line.

All that is required to provide enablement is that any mode of making and using the invention be recited in the specification. Engel Industries, Inc. v. Lockformer Corp., 946

F.2d 1528, 20 U.S.P.Q. 2d 1300 (Fed. Cir. 1991). This standard is clearly met here by the working example described above. This working example is readily reproducible.

A review of the factors set forth by the Federal Circuit in In re Wands, 858 F.2d 731, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988) is useful. These factors are: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. Id.

A review of these factors indicates that enablement is present and there is no basis for a rejection on the grounds of lack of enablement under the first paragraph of 35 U.S.C. § 112. This supports reversal of the rejection made by the Examiner.

The quantity of experimentation required is not excessive in view of the subject matter and the known properties of the Kohler-Milstein process for the production of monoclonal antibodies. Johns Hopkins University, 152 F.2d at 1360, 47 U.S.P.Q. 2d at 1705. Again, a process for the production of monoclonal antibodies that is initiated by immunization of an antibody-producing animal with a purified antigen covalently linked to a carrier protein should be even more reproducible than a process for the production of monoclonal antibodies that is initiated by immunization of an antibody-producing animal with an intact cell line.

The amount of direction or guidance presented in the specification is substantial. Exact details are presented for the preparation of the immunogen, including the method of making the derivative of tacrolimus and the coupling of the tacrolimus to a suitable carrier. Additionally, details are presented on the screening of the monoclonal antibodies produced. A working example is present. The monoclonal antibody 1H6 is described. This monoclonal antibody was produced according to the methods recited in the specification and meets the claim limitations. Nothing more is required for enablement of the claims at issue.

The nature of the invention is such that undue experimentation is not present. The claimed invention, from the standpoint of enablement, is of a relatively restricted scope. The antibody binds a specific antigen and not a possible range or genus of antigens. Moreover, the functional language recited in the claims in terms of affinity and cross-reactivity must be taken into account in evaluating the existence of enablement. In re Halleck, 422 F.2d 911, 164 U.S.P.Q. 647 (C.C.P.A. 1970). This language excludes inoperative embodiments from the scope of the claims.

The state of the prior art suggests that what experimentation would be required is routine. Although the prior art here is not relevant with respect to the patentability of the invention, it does suggest that the Kohler-Milstein technique for preparing monoclonal antibodies by cell fusion is well understood and whatever experimentation is required is routine. Johns Hopkins University, 152 F.2d at 1360, 47 U.S.P.Q. 2d at 1705. As emphasized above, this is a well-studied technique and its application would be routine to produce monoclonal antibodies beginning with a purified antigen covalently linked to a carrier.

The relative skill of those in the art is relatively high. This invention is directed to Ph.D. biochemists or immunochemists or M.D.'s with extensive research experience. These individuals are well-versed in the relevant technology and know-how so that they can perform such procedures. This point was emphasized in Johns Hopkins University. The failure of individuals lacking the required skill to reproduce the claimed invention was disregarded by the court.

The predictability or unpredictability of the art does not lead to a conclusion of nonenablement. The limited degree of unpredictability of the Kohler-Milstein process for the production of monoclonal antibodies does, as emphasized above, not lead to a conclusion that these claims are not enabled. There is simply no basis for such a conclusion in view of the specification and the presence of a working example. There is no evidence or reasoning

presented that would lead one to the conclusion that the claims are not enabled. The only basis provided for this is an assertion of unpredictability with no supporting reasoning and no technical evidence.

The breadth of the claims strongly argues for enablement. The claims are directed to monoclonal antibodies that bind a single, specific antigen with defined limits as to affinity and cross-reactivity. These monoclonal antibodies do not bind a range of antigens or analogues of the antigen. They bind a specific, defined antigen that is an identified chemical compound. Moreover, the functional language in the claims in terms of the cross-reactivity and affinity must be taken into account in determining the scope of the claims and the existence of enablement. In re Halleck, 422 F.2d at 911, 164 U.S.P.Q. at 647. These are not claims for which a degree of extrapolation is required such that the extrapolation would lead to undue experimentation. Compare In re Strahilevitz, 668 F.2d 1229, 212 U.S.P.Q. 561 (C.C.P.A. 1982) with In re Fisher, 427 F.2d 833, 166 U.S.P.Q. 18 (C.C.P.A. 1970) (no enablement for claims to an ACTH preparation having a potency of at least 1 international unit/mg, with no upper limit, when specification discloses preparation of ACTH of potency between 1.11 and 2.30 international units/mg). Here, the scope of the protection sought is relatively circumscribed and the degree of experimentation required is minimal in view of the well-understood subject matter of the claims.

In fact, the Federal Circuit itself, in Wands, found that enablement existed and that undue experimentation was not present. It held that "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 858 F.2d at 737, 8 U.S.P.Q. 2d at 1404.

The evidence strongly indicates that the amount of experimentation required to reproduce the claimed subject matter would be routine. Moreover, the specification provides a great deal of detailed guidance with respect to the experimentation that might be required. The methods of preparation of the immunogen are set out precisely. The immunization schedule is

also set out precisely. The screening method is described in detail as to both the reagents to be bound to the solid support in the ELISA assay and the detection method. The other steps in the process required, namely the cell fusion and cloning, are performed by standard methods as part of the well-understood Kohler-Milstein procedure.

A careful review of the conclusions of In re Wands indicates that enablement is present, as was held in that case itself. This is logical in view of the state of the art and the subject matter of the application.

The sole ground for lack of enablement appears to be the recitation of only a single working example. That ground is legally insufficient.

The United States Patent and Trademark Office training materials for examining patent applications with respect to enablement clearly state that a rejection for lack of enablement should not be made solely on the grounds that only one working example is present. "The presence of only one working example should never be the sole reason for making a scope rejection, even though it is a factor to be considered along with all the other factors. To make a valid rejection, one must evaluate all the facts in evidence and state why one would not expect to be able to extrapolate that one example across the entire scope of the claims." Training Materials for Examining Patent Applications with Respect to 35 U.S.C. Section 112, First Paragraph – Enablement Chemical/Biotechnical Applications, *reprinted in* 2 Iver P. Cooper, *Biotechnology Law*, App. H-156, App. H-177 (2000).

Similarly, the Manual of Patent Examining Procedure strongly emphasizes that the presence of one working example cannot be the sole basis for a lack of enablement rejection under the first paragraph of 35 U.S.C. § 112. M.P.E.P § 2164.01(c).

A representative example is sufficient to enable a claimed genus. M.P.E.P § 2164.01(c).

> For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation. Id.

The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. In re Buchner, 929 F.2d 660, 18 U.S.P.Q. 2d 1331 (Fed. Cir. 1991); Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987).

As long as the specification discloses at least one method for making and using the claimed invention that bears a "reasonable correlation" to the entire scope of the claim, the enablement requirement of the first paragraph of 35 U.S.C. § 112 is satisfied. In re Fisher, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (C.C.P.A. 1970).

In the Advisory Action, the Examiner stated: "[T]he hybridoma 1H6 which is required for the production of the claimed monoclonal antibody is not recited in claim 11 and a deposit in accordance with the Budapest treaty has not been made for the hybridoma." (Advisory Action of March 6, 2002, Continuation of ¶ 5). This statement would be significant only if this hybridoma were the only hybridoma that could be used by one of ordinary skill in the art without undue experimentation to produce the antibody of claim 11. The foregoing discussion has established that this is clearly not the case. One of ordinary skill in the art could make additional hybridomas that produced an antibody having the properties of the antibody of

claim 11 without undue experimentation. Therefore, there is no need for a deposit of the hybridoma 1H6, whether in accordance with the Budapest Treaty or not.

No deposit of a hybridoma is required if the required biological materials, that is, a hybridoma that produces a monoclonal antibody that meets the requirements of claim 11, can be obtained from publicly available material with only routine experimentation and a reliable screening test. Tabuchi v. Nubel, 559 F.2d 1183, 194 U.S.P.Q. 521 (C.C.P.A. 1977); Ex parte Hata, 6 U.S.P.Q. 2d 1652 (Bd. Pat. App. & Int'f 1987). Similarly, no deposit of a hybridoma was required in In re Wands, 858 F.2d 731, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988) because it was held that no undue experimentation would have been required for one of ordinary skill in the art to make hybridomas that produced monoclonal antibodies that produced high-affinity IgM antibodies against hepatitis B surface antigen. The starting materials required were available to the public, and the basic techniques used for cloning and screening the hybridomas were well-known to the public or had been described in the specification. Thus, enablement was present and the requirement for a deposit had been obviated. Id.

The situation here is exactly analogous to that of Wands. The starting materials, including tacrolimus and a carrier such as keyhole limpet hemocyanin, are readily available. The procedures for immunization, cell fusion, cloning, and screening are either disclosed in the specification in detail or are well-known in the art. The failure to deposit the hybridoma designated in the specification as 1H6 and the failure to recite that hybridoma in the claim cannot lead to a conclusion of lack of enablement. No deposit is required, and the claims cannot be read, in view of the specification, the claim language itself, and the state of the art, to be limited to the specific hybridoma 1H6.

What is in fact lacking in the rejection is an evaluation of all the facts in evidence and a statement as to why one would not be able to extrapolate that one example across the entire scope of the claims. The entire rejection has been predicated on the existence of only one

working example. That is legally insufficient according to Patent and Trademark Office policy and squarely contravenes the application of the factors of Wands.

Specifically, there has been absolutely no evidence presented that any step in the procedure required to produce a monoclonal antibody that had the properties of the monoclonal antibody of claim 11 of the present invention would require undue experimentation or could not be performed by one of ordinary skill in the art. There has been no suggestion that the coupling procedure to produce a conjugate of tacrolimus and a carrier protein would be irreproducible or inoperative. There has been no suggestion that the production of polyclonal antibodies using the conjugate as an immunogen would be irreproducible or even difficult. There has been no suggestion that the cell fusion process using cells producing the polyclonal antibodies and a suitable fusion partner would be inoperative or irreproducible. There has been no suggestion that the cloning or screening procedures used would be inoperative or irreproducible. The sole basis of the rejection by the Examiner has been that only one working example has been provided and that the generation of another hybridoma that produced a monoclonal antibody that met the requirements of claim 11 would require undue experimentation. No basis whatsoever has been provided for this conclusion of undue experimentation.

Accordingly, the Board of Patent Appeals and Interferences is respectfully requested to reverse the rejection and require that the pending claims be passed to issue.

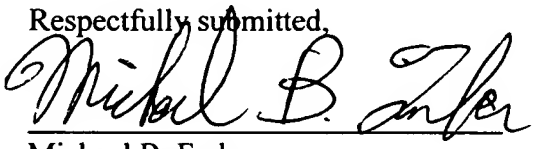
IX. PENDING CLAIMS

Claims 11-12, 31-33, 50-51, and 61 are pending. A copy of all claims currently pending in the application under appeal is provided in the Appendix to this brief.

X. CONCLUSION

In conclusion, all claims remaining for consideration are patentable. These claims meet the standards required for enablement under the first paragraph of 35 U.S.C. § 112. Accordingly, the Board of Patent Appeals and Interferences is respectfully requested to reverse the rejection of all claims and to remand this case for further prosecution with directions to allow all pending claims.

Respectfully submitted,



Date: April 24, 2002

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APPENDIX

PENDING CLAIMS

The following claims are pending in the above-identified application.

11. (Once amended) A monoclonal antibody to tacrolimus produced by a hybridoma produced by fusion of antibody-producing cells from an antibody-producing mammal immunized with tacrolimus derivatized with a carboxymethyl oxime moiety at carbon atom 22 coupled to a high molecular weight protein with a suitable fusion partner, that has a binding affinity for tacrolimus of about 3.7×10^9 liters/mole, that cross-reacts with 13-demethyl tacrolimus, and that has less than about 8% cross-reactivity to all of the following tacrolimus metabolites: 15-demethyl tacrolimus; 31-demethyl tacrolimus; 13,31-didemethyl tacrolimus; 15,31-didemethyl tacrolimus; and 12-hydroxy tacrolimus.

12. The monoclonal antibody of claim 11 wherein the high molecular weight partner is keyhole limpet hemocyanin.

31. A conjugate comprising the antibody of claim 11 conjugated directly or indirectly to a detectable label.

32. The conjugate of claim 31 wherein the detectable label is selected from the group consisting of an enzyme label, a radioactive label, a fluorescent label, a chemiluminescent label, a bioluminescent label, and a particulate label.

33. The conjugate of claim 32 wherein the detectable label is an enzyme label.

50. A method of detecting or determining tacrolimus comprising the steps of:

(a) providing a sample suspected of containing tacrolimus;

(b) reacting the sample with:

(i) the antibody of claim 11; and

(ii) optionally, a tacrolimus analogue; wherein one of the antibody or the tacrolimus analogue is labeled with a label producing a detectable signal;

(c) observing or measuring one of:

(i) the signal associated with tacrolimus bound to antibody;

(ii) the signal associated with tacrolimus unbound to antibody; and

(iii) the total signal present;

in order to detect or determine the presence or concentration of tacrolimus in the sample.

51. The method of claim 50 wherein the sample is reacted with a tacrolimus analogue labeled with an enzyme label and the total signal present is observed or measured to detect or determine the presence or concentration of tacrolimus in the sample.

61. A test kit comprising, packaged in separate containers:

(a) the antibody of claim 11; and

(b) a tacrolimus analogue labeled directly or indirectly with an enzyme label.

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DATE 04-23-02

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OUR REF. #	INVOICE DATE	INVOICE NO.	C/M # CHGD.	DESCRIPTION	NET CK. AMT.
383355	04-23-02	14598.41	014598-000041	FEE FOR FILING A BRIEF IN	320.00

VENDOR: COMMISSIONER OF PATENTS 26600 TOTAL CK $ ***** 320.00